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CASE REPORT

Syncope Following Treatment of UTI: A Case of Acute Hemolytic Anemia, Methemoglobinemia and Acute Renal Dysfunction Following Phenazopyridine Use in a Patient With G6PD Deficiency

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive genetic disorder which commonly affects males. It is due to a defect in the red blood cell enzyme, G6PD. Lack of G6PD makes the RBCs vulnerable to oxidant stress resulting in hemolysis. The severity of hemolytic anemia varies among individuals with G6PD deficiency. Here we present a case of an 80-year-old man admitted with syncope and jaundice. He was treated with phenazopyridine for a UTI 2 weeks ago. Subsequent investigation revealed G6PD deficiency as well as methemoglobinemia. Historically, phenazopyridine has been associated with causing methemoglobinemia and triggering hemolysis in G6PD deficient individuals. However, only a few cases have been reported in the last 60 years, making it a very rare occurrence.

Keywords: G6PD deficiency, Hemolytic anemia, Methemoglobinemia, Acute kidney failure

1. Case presentation

An 80-year-old Russian male with a past medical history of hypertension, benign prostatic hyperplasia, and hypothyroidism, presented to the ED with complaint of a witnessed episode of loss of consciousness lasting for a few minutes. The episode was not associated with trauma, prodrome, seizure or postictal confusion. Prior to this, the patient also had bilateral flank pain for about 8 days and had been started on treatment for a urinary tract infection with phenazopyridine and antibiotics 10 days prior. For several years his home medications had included tamsulosin, amlodipine, lisinopril and levothyroxine. Patient also reported an episode of jaundice which he had experienced 40 years ago that had resolved on its own.

On physical examination, the patient was in no active distress and was sitting comfortably on the bed. He was alert and oriented to time, place and person. His vital signs were normal. Full neurological examination was unremarkable but systemic examination was significant for scleral icterus and diffuse yellowing of the skin. On abdominal examination, his liver span was normal, spleen and kidneys were not palpable. There was no CVA tenderness as well as no lymphadenopathy.

CT head without contrast ruled out acute intracranial pathology. Baseline investigations were ordered. The significant lab test and their results are mentioned in Table 1:

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Table 1. Baseline lab investigations.

Hematological investigations	Results
Hemoglobin	6.8 (14–18 gm/dL)
Hematocrit	21 (42–52%)
MCV	100 (80–94 fL)
Reticulocytes	4 (0.5–1.5%)
Creatinine	89 (7–21 mg/dL)
BUN	5.5 (0.5–1.3 mg/dL)
Total Bilirubin	8.2 (0.2–1.4 mg/dL)
Direct Bilirubin	0.9 (0.0–0.2 mg/dL)
Serum Ferritin	1648 (3–111 ng/ml)
Serum Folate	6 (>6.6 ng/ml)

AST, ALT, serum iron, TIBC and transferrin were normal. Because of the unconjugated hyperbilirubinemia and anemia, a complete hemolytic anemia workup was done. **Coombs's test was negative, serum LDH was high, and serum haptoglobin was within normal limits. A high methemoglobin level was also present, 2.1 (0.2–0.6%).** Peripheral smear showed some rare spherocytes, minimal hypochromia and occasional bite cells (Fig. 1). Negative SPEP, UPEP and immunofixation ruled out multiple myeloma.

Due to unconjugated hyperbilirubinemia coupled with hemolytic anemia, acute renal failure, and methemoglobinemia, acute hemolysis due to G6PD deficiency was suspected which was confirmed when **G6PD levels were extremely low, 2.3 (7–20.5 U/g Hgb).** It was also suspected that the patient's similar episode of jaundice 40 years ago was also due to an acute attack of hemolysis due to underlying G6PD deficiency.

The patient received blood transfusion, IV fluids for acute renal failure and folate. Any drug that could trigger hemolysis was avoided. The patients' hemoglobin, BUN and creatinine, intake and output were closely monitored over the next few days. Once the renal function normalized and hemoglobin was stable, the patient was discharged with a clear set of instructions indicating which drugs and foods were to be avoided to prevent a similar episode of jaundice and anemia.

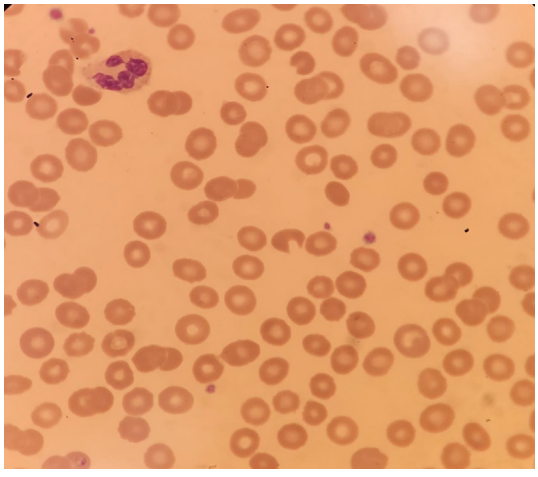

Fig. 1. Rare spherocytes, minimal hypochromia and some bite cells.

2. Discussion

Phenazopyridine, a drug used for dysuria in the setting of a UTI, has historically been a well-known drug to avoid in patients with G6PD deficiency. But only a handful of cases have been reported in the last 50 years which prove such association. Gabor et al., in 1964 reported a case of a 79-year-old woman who developed a Heinz body hemolytic anemia while being treated for a UTI with pyridium.[1] They reported normal G6PD levels in the patient's RBCs and deduced that the drug could cause hemolysis in both G6PD deficient and non-G6PD deficient RBCs. Galun et al., Tishler et al., and Mercieca et al., reported cases of phenazopyridine induced acute hemolysis in patients with G6PD deficiency in the latter half of the 20th century and advised that the drug be avoided in all patients with G6PD deficiency.[2-4] According to our literature search, only one article written by Greenberg et al., in 1964 reported methemoglobinemia and Heinz body hemolytic anemia due to phenazopyridine use but both their subjects had normal Glutathione levels in the RBCs.[5] In recent years, Ghimire et al., reported a case of a woman of northern European descent who developed shortness of breath after being treated with nitrofurantoin and phenazopyridine for a UTI.[6] She was found to have hemolytic anemia due to G6PD deficiency, which resolved once the offending agents were discontinued.

Although G6PD deficiency is global in its distribution, most cases are seen in Kurdish Jews, Sardinians and Nigerians.[7-9] As G6PD deficiency is an X-linked disease, most men are affected by it because of their homozygosity. As a result, all their RBCs will be affected. Females who inherit G6PD deficiency are carriers of the disease, as half of their RBCs have the normal G6PD allele and half have the abnormal allele. However, the cells which express the abnormal allele can undergo hemolysis just like the G6PD deficient RBCs in males. In case of skewed lyonization, females with G6PD deficiency can have similar presentations as those seen in males.[10]

G6PD deficiency is the most common enzyme disorder of the RBCs. Individuals with G6PD deficiency in their RBCs are not able to produce NADPH from NADP. This conversion is essential

Table 2. Variants of G6PD deficiency.

Variant	Severity of enzyme deficiency	Clinical Presentation
Class 1	Severe (<10% of normal)	Associated with chronic hemolytic anemia
Class 2 (Mediterranean and Asian variant)	Severe (<10% of normal)	Intermittent hemolysis usually due to minor exposure to oxidative stress (drugs or fava beans)
Class 3 (G6PD A^- variant, the most common variant seen in people of African descent)	Moderate (10–60% of normal)	Intermittent hemolysis mostly due to significant oxidative stress
Class 4	No enzyme deficiency or hemolysis	None
Class 5	Increased enzyme activity	None

for the formation of glutathione, an antioxidant that protects RBCs from different oxidative stressors. As a result, due to deficiency of glutathione, the different reactive oxygen species generated by different oxidative stressors lead to hemolysis of RBCs.[11]

Many different variants of G6PD deficiency have been described until now. The World Health Organization has classified these variants based on enzyme deficiency and the resulting severity of hemolysis[12,13] (Table 2).

There are many drugs which have been known to cause hemolysis in G6PD deficient individuals. Chlorpropamide, chloramphenicol, fluoroquinolones, dapsone, nitrofurantoin, phenazopyridine, sulfonylurea, primaquine, rasburicase and pegloticase, methylene blue and nalidixic acid should be avoided or used with extreme caution.[14] Moreover, some food items and herbs like fava beans, camphor, menthol, naphthalene and henna are notorious for triggering acute hemolysis.[15] Ingestion of fava beans produces highly reactive redox compounds, which enter the bloodstream causing oxidative stress leading to hemolytic anemia. This phenomenon is called favism and is strongly linked to acute hemolysis in G6PD deficiency, seen mostly in boys ranging from 1 to 5 years of age.[16]

Clinically, patients with G6PD deficiency can present at any stage of their lives. Neonates usually present with pathological jaundice with signs and symptoms of lethargy, irritability, yellowing of the skin, sclera and mucous membranes, vomiting, poor feeding and fever. Kernicterus can also ensue which can prove to be fatal if not treated. Hence atypical neonatal jaundice should raise suspicion of G6PD deficiency.[13] Children and adults usually exhibit similar signs and symptoms of hemolytic anemia due to G6PD deficiency. They include fatigue, irritability, pallor, jaundice, dark urine, abdominal pain, tachycardia, shortness of breath, flank and back pain and renal failure. Some patients can also have methemoglobinemia and present with cyanosis, seizures, arrhythmias, and in some cases, death.[17]

Patients with G6PD deficiency have all the features of hemolytic anemia. During an acute attack of hemolysis, their hemoglobin drops resulting in reticulocytosis. Coombs's test is negative, and serum haptoglobin and LDH can also point in the right direction. Peripheral smear can narrow down the differential and show Heinz bodies in RBCs which are formed due to oxidative denaturation of hemoglobin. As the Heinz bodies pass through the liver and spleen, the macrophages ingest them, causing bite cells to form. Both Heinz bodies and bite cells, when seen in a peripheral smear, are indicative of G6PD deficiency.[6] Multiple tests can be performed to arrive at the final diagnosis. They usually consist of an initial qualitative screening test and a quantitative confirmatory test.[13] The timing of the G6PD assay is essential as during an acute hemolytic attack, all RBCs deficient in G6PD are removed and replaced by new erythrocytes and reticulocytes hence G6PD levels may be falsely normal or elevated during an acute attack.[6] Blood transfusions may also raise the G6PD level. Hence it is advised to perform the G6PD assay at least 3 months after an acute attack to obtain an accurate estimate of G6PD levels. The treatment of hemolysis in G6PD deficiency revolves around discontinuing the offending agent or treating the acute illness responsible for triggering the hemolytic attack. Patients with severe hemolysis and rapid drop in hemoglobin will benefit from blood transfusions which can be lifesaving. Other patients with renal failure and shock will require IV fluids to become hemodynamically stable.

3. Conclusion

G6PD deficiency makes RBCs susceptible to oxidant stress leading to acute hemolysis in the presence of certain drugs, acute illnesses, and food items. Phenazopyridine has always been on that list for the past 60 years, but only a handful of actual

cases of hemolysis due to its use in G6PD deficient individuals have been reported in the literature. It not only causes hemolysis in G6PD deficiency, but it can also lead to methemoglobinemia, which can be fatal if not treated timely. Its use should be avoided in patients with G6PD deficiency, and it should be discontinued as soon as any signs of hemolysis becomes visible.

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Conflict of interest

The authors declare no conflict of interest.

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